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CHLAMYDIA TRACHOMATIS INFECTIONS

Policy Guidelines for Prevention and Control

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CONTENTS

These policy guidelines for the prevention and control of Chlamydia trachomatis *infections were established after careful deliberation by a group of experts* and staff of the Centers for Disease Control (CDC).† Commentary received after preliminary documents were circulated among a large group of physicians was also considered. Certain aspects of these guidelines represent the best judgment of experts. The guidelines should not be construed as rules, but rather as a source of guidance within the United States. This is particularly true for topics that are based on limited data.*

Background

Infections caused by *Chlamydia trachomatis* are now recognized as the most prevalent—and are among the most damaging—of all sexually transmitted diseases (STD) seen in the United States today (*1*). An estimated 3-4 million Americans suffer from a chlamydial infection each year (*2*). Men, women, and infants are affected, but women bear an inordinate burden because of their increased risk for adverse reproductive consequences. While *C. trachomatis* infection is currently not a reportable disease on a national level in the United States, data obtained from metropolitan STD clinics suggest sharp increases in incidence in the period 1975-1983 (*1*). In England and Wales, where nongonococcal urethritis (about half the cases of which are caused by *C. trachomatis*) is a reportable disease, the incidence has nearly doubled in the last decade (*1*).

Chlamydiae are unique microorganisms whose specific properties have been delineated largely in the last two decades. Although they are classified as bacteria, they share properties with viruses and bacteria. Like viruses, chlamydiae grow only intracellularly. For this reason, culture of *Chlamydia* has been difficult because expensive cell-culture methods similar to those used to recover viruses are required. Unlike viruses, however, chlamydiae contain both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), divide by binary fission, and have cell walls similar to those of gram-negative bacteria.

The wider availability of laboratory diagnostic tests for *Chlamydia* has opened the door to further exploration of the broad spectrum of disease caused by this organism. *C. trachomatis* is now recognized as the causative agent for a diverse group of genital and neonatal infections, including many that were previously considered to be of unknown cause (*1,3,4*) (Table 1).

C. trachomatis causes approximately 50% of the reported cases of nongonococcal urethritis (NGU) among men. This STD has an estimated incidence 2.5 times that of gonococcal urethritis (*1*). *Chlamydia* is also responsible for approximately 50% of the estimated 500,000 cases of acute epididymitis seen each year in the United States (*2*).

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†Background information for these guidelines was developed in collaboration with faculty and staff of the Institute for Health Policy Studies, School of Medicine, University of California, San Francisco.

Even more important are chlamydial infections among women. Most of these infections are asymptomatic, but *C. trachomatis* also plays an important role in causing mucopurulent cervicitis (MPC) (*5*), acute pelvic inflammatory disease (PID) (*6*), and maternal and infant infections during pregnancy and following delivery (*7*). *Chlamydia* accounts for one-quarter to one-half of the 1 million recognized cases of PID in the United States each year. These infections, in addition to *C. trachomatis* infections of the fallopian tube not clinically recognized as PID, contribute significantly to the increasing number of women who experience ectopic pregnancy or involuntary infertility. Besides its association with mucopurulent cervicitis and PID, *Chlamydia* plays an important role in the urethral syndrome (dysuria-pyuria syndrome) and in perihepatitis or Fitz-Hugh-Curtis syndrome (*1,8*).

Maternal infection during pregnancy has been associated with postpartum endometritis and in some studies with an increased perinatal mortality; the latter relationship requires further study. Infants with infected mothers can acquire a chlamydial infection at birth from contact with infected cervicovaginal secretions. Each year more than 155,000 infants are born to *Chlamydia*-infected mothers. These newborns are at high risk of developing inclusion conjunctivitis and pneumonia and are at slightly elevated risk of having otitis media and bronchiolitis. In fact, *Chlamydia* is the most common cause of neonatal eye infections and of afebrile interstitial pneumonia in infants < 6 months of age.

Enormous cost is associated with chlamydial infections. Each year, more than $1 billion in direct and indirect costs are expended on these infections in the United States. Many of these

TABLE 1. Clinical spectrum of *Chlamydia trachomatis* infections*

Males† ⇄ Females† → Infants		
Infections§	**Infections§**	**Infections§**
Urethritis	Cervicitis	Conjunctivitis
Post-gonococcal urethritis	Urethritis	Pneumonia
Proctitis	Proctitis	Asymptomatic pharyngeal carriage
Conjunctivitis	Conjunctivitis	Asymptomatic gastrointestinal tract carriage
Pharyngitis?	Pharyngitis?	Otitis media?
Subclinical lymphogranuloma venereum	Subclinical lymphogranuloma venereum	
Complications§	**Complications§**	
Epididymitis	Salpingitis	
Prostatitis?	Endometritis	
Reiter syndrome?	Perihepatitis	
Sterility?	Ectopic pregnancy	
Rectal strictures¶	Infertility	
	Dysplasia?	
	Postpartum endometritis?	
	Prematurity?	
	Stillbirth?	
	Neonatal death?	
	Vulvar/rectal carcinoma?¶	
	Rectal strictures¶	

*Trachoma, the leading cause of preventable blindness in the world, is also caused by *Chlamydia* but has been excluded because it is not generally sexually transmitted.

†Arrow indicates direction of transmission of infection.

§Question mark indicates that a relationship has not been firmly established.

¶Associated with lymphogranuloma venereum.

costs result from the management of women with PID and its complications (*9*) and from the management of infants hospitalized with chlamydial pneumonia. This estimated cost does not reflect the human suffering experienced by those with chlamydial disease. Further growth in the economic burden of chlamydial infections will occur as these infections become more prevalent.

To reduce the morbidity and subsequent complications associated with *C. trachomatis* infection in the United States, effective prevention and control strategies must be implemented. Comprehensive guidelines for the formulation of such control programs, as well as diagnostic and therapeutic approaches to infected individuals, are provided in this document. These policy guidelines were established after careful deliberation by an invited panel of experts in collaboration with staff of the Division of Sexually Transmitted Diseases, CDC.

Risk Assessment

Establishing a profile for patients at increased risk of having a genital infection caused by *C. trachomatis* can be based on multiple criteria.

Individual Characteristics and Practices

Age, number of sex partners, socioeconomic status, and sexual preference are predictors of *C. trachomatis* infection. Genital infection rates appear to be inversely related to age and positively correlated with number of sex partners. Sexually active women < 20 years of age have chlamydial infection rates 2-3 times higher than those for women ≥ 20 years of age, and the rates for women ages 20-29 are considerably higher than those for women ≥ 30 years of age (*1,10*). Similarly, the rates of urethral infection among teenage males are higher than those for adults (*11*). Risk of infection increases with the number of sex partners (*12,13*). In some studies, lower socioeconomic status and ethnicity have been correlated with an increased risk of chlamydial infections (*10-12*). The prevalence of urethral chlamydial infection among homosexual men is approximately one-third the prevalence among heterosexual men (*11,14*), but 4%-8% of homosexual men seen in STD clinics have rectal chlamydial infection.

Clinical Syndromes

Several clinical syndromes are associated with *C. trachomatis* infection. Some are more clearly defined than others, and their prevalence and manifestations differ depending on the population studied. Nevertheless, these conditions often provide the most suitable basis for initiating treatment, especially if complete bacteriologic evaluation is not possible or while the practitioner awaits the results of specific laboratory tests. However, it cannot be overemphasized that most women with cervical chlamydial infection, most homosexual men with rectal chlamydial infection, and as many as 30% of heterosexual men with chlamydial urethritis have few or no symptoms. These asymptomatic infections can sometimes be recognized by physical examination or by increased numbers of leukocytes on a Gram stain of infected secretions.

Three *Chlamydia*-associated syndromes* are common among women: (1) MPC, (2) urethral syndrome or urethritis, and (3) PID. *C. trachomatis* has been isolated from 30% to 50% of women examined who have mucopurulent endocervical exudate (*5*). Similarly, *C. trachomatis*

*For a more complete description of syndromes, see section on Treatment Regimens, pages 65S-67S.

has been isolated from female patients with acute dysuria, particularly those with pyuria and a negative Gram stain of unspun urine (*8*). Among women with PID, the *Chlamydia* recovery rate is approximately 25%-50% with optimal technique, but serologic data suggest that as many as 50% of acute PID cases may be associated with *C. trachomatis*.

Two *Chlamydia*-associated syndromes are common among men: nongonococcal urethritis (NGU) and acute epididymo-orchitis. *C. trachomatis* has been consistently isolated from up to 50% of men with NGU. Likewise, investigators have cultured *C. trachomatis* from 30% to 50% of patients with acute epididymitis and have demonstrated the organism to be the leading known cause of epididymitis among men < 35 years of age (*1*).

Contact with an STD Patient

Individuals with a history of sexual exposure to persons with a chlamydial or gonococcal infection are themselves at high risk for chlamydial infection. Approximately 70% and 36%, respectively, of female sex partners of men with confirmed chlamydial urethritis or confirmed gonococcal urethritis have *Chlamydia* isolated from the endocervical tract. Of all the women whose sex partners are reported to have NGU, 30%-40% harbor cervical chlamydial infection. Of men who are the sex partners of women with confirmed chlamydial MPC or PID, 25%-50% have *Chlamydia* isolated from the urethra. Many of these contacts are asymptomatic.

Coexistence of Chlamydial Infection with Other STD

Approximately 15%-30% of heterosexual men with gonococcal urethritis have simultaneous urethral infection caused by *C. trachomatis* (*1,15,16*). An even higher proportion (25%-50%) of women with *Neisseria gonorrhoeae* infection also have *C. trachomatis* infection of the cervix (*1,15-17*). Women who have other STD such as trichomoniasis and bacterial vaginosis are also at increased risk of having chlamydial infection.

Method of Contraception

Persons who use barrier methods of contraception (condom, diaphragm, diaphragm and foam) are at reduced risk for chlamydial infection relative to those who do not use any form of contraception (*12*). In contrast, women who use oral contraceptives have been reported to have a higher prevalence of cervical infection with *C. trachomatis* than women who do not use oral contraceptives (*18*). Use of intrauterine devices has not yet been investigated for its effect on rates of *C. trachomatis* infection.

Pregnancy

In the United States, the prevalence of reported cervical chlamydial infection among pregnant women has varied from 2% to 37%, with most studies reporting infection rates of approximately 8%-12% (*1,13,19*). In general, infection has been most prevalent in the youngest age group; among unmarried women; and among inner-city, lower socioeconomic-status women.

Health-Care Facility

Various types of health-care facilities will report different expected infection rates among women attendees. Not surprisingly, STD clinics report the highest rates of *C. trachomatis* infection (an average of 20%-30% of all patients tested) (*1,15*). The next highest isolation rates are reported from clinics for adolescent patients (8%-26%) (*13,20-23*) and from family planning clinics (6%-23%) (*10*). Insufficient data are available to estimate expected rates in private practices, community health centers, and hospital emergency rooms.

Laboratory Methods

The absence of an inexpensive, simple, and reliable diagnostic test for chlamydial infection has limited control efforts. Historically, time-consuming and expensive tissue-culture techniques have been required to definitively diagnose most *C. trachomatis* infections. Cytology was also available, but is only of comparable sensitivity to tissue culture in diagnosing newborn conjunctivitis. In recent years antigen detection methods have offered a cost-effective alternative to culture. Serologic methods are available, but remain principally a research tool.

Despite these encouraging improvements in diagnostic capability, current tests are not ideal. They are relatively difficult to perform, require considerable experience, and have limited application. Active investigation of new diagnostic methods for *C. trachomatis* continues, and antigen and antibody detection systems are improving rapidly. In such a dynamic environment, recommendations for the specific diagnostic methods discussed below must be flexible and should be revised as better methods become available.

Culture

Tissue culture is presently the "gold standard" for laboratory diagnosis. Although published methods are fairly standard (*4*), in practice many laboratories introduce variations that alter the sensitivity and specificity of the test. Rigorous adherence to standard methodology is strongly encouraged.

Two major components are needed to culture for *C. trachomatis*: (1) a cell-culture system and (2) a method to identify inclusions growing in cell culture. The cell line of choice is McCoy. Alternatively, a particular strain of HeLa cells (HeLa 229) (*24*) can be used, but is usually restricted to research laboratories. Specimen material is centrifuged onto the cells for 1 hour and then incubated for 2-3 days in medium containing cycloheximide (*25*). Incubation can take place in individual vials with cover slips at their base or on flat-bottomed wells in plastic microtiter plates (*26*). The choice between these methods is generally dictated by the number of specimens a laboratory has to process; the vial method is slightly more sensitive and less susceptible to cross-contamination, but is more time-consuming and expensive.

For identification, either iodine stain or fluorescent antibody (FA) stain are usually used. FA stain offers the advantages of higher sensitivity and shorter processing time (2-3 days), but requires a fluorescence microscope. The standard method for iodine staining requires one blind passage, which increases the processing time to 4-6 days. In microtiter plates, FA staining without passage appears equivalent to iodine staining with one blind passage (*27*). The most sensitive culture method currently available involves using cycloheximide-treated McCoy cells in vials in the presence of fluorescent monoclonal antibodies.

Compared with other diagnostic tests for *C. trachomatis*, the major advantage of tissue culture is its specificity. With this method, the organism can also be positively identified or saved for other marker studies such as immunotyping. Thus, culture is clearly the method of choice for research studies. Determining the sensitivity and specificity of the culture has not been possible since it is the reference standard for other methods; however, it is estimated that culture has a sensitivity of 80%-90%, and a specificity of 100% (*28*).

Culture also has several disadvantages: (1) the cost and complexity of laboratory requirements can be prohibitive; (2) specimens can be kept at 4 C for only up to 24 hours (preferably 12) before processing, or frozen at -70 C if they cannot be inoculated within 24 hours; (3) specimens must be placed in specially prepared transport media; and (4) the cell monolayer may be contaminated with other bacteria or viruses, particularly in vaginal or rectal specimens.

Cytologic Methods

Cytologic identification of chlamydial infections—the only method available in the period 1909-1957—is an examination of epithelial cell scrapings (e.g., conjunctival, cervical, urethral) on a stained smear. A modified Giemsa stain is most often used, although Wright's and other standard tissue stains can be used. Infection is identified by visualizing characteristic intracytoplasmic inclusions. Alternatively, cell scrapings can be examined using FA stains (*4*).

The advantage of cytologic examination is clearly the simplicity of the process, particularly if light microscopy is used. The disadvantage is the poor sensitivity for diagnosing chlamydial infections other than neonatal conjunctivitis, for which the sensitivity of cytology compared with culture is 95%. The sensitivity of cytologic methods in identifying chlamydial adult conjunctivitis is 45% for Giemsa and 85% for FA. In tests for cervical infection, the two stains have sensitivities of only 40% and 65%, respectively, and for urethral infection, 15% and 60% (*28*). Moreover, these upper levels of sensitivity can only be obtained with good specimens (many epithelial cells) and an experienced observer.

Thus, standard cytology is of little practical value as a diagnostic aid for genital chlamydial infection. However, two recent studies (*29,30*) suggest that the inflammatory pattern on Papanicolaou-stained cervical smears may be useful when it is used as a screening test to select patients for confirmation of infection by culture or monoclonal antibody tests, but the Papanicolaou method used alone is not satisfactory for diagnosing chlamydial infection.

Antigen Detection

To date, two methods of antigen detection are available: (1) FA examination of a direct smear and (2) enzyme immunoassay (EIA). One example of each method is presently available commercially,* and both have undergone considerable evaluation.

However, continued revision of these tests takes place even after they become available commercially. Consequently, initial published data on efficacy may be outdated, so the most recent references should be used. Other antigen detection tests are expected to be available soon.

Direct-Smear FA Test (*31*)

With this procedure, specimen material is obtained by swab and applied directly to a slide, which is fixed and then incubated with fluorescein-conjugated monoclonal antibody before being examined under a fluorescence microscope. Total processing time is usually 30-40 minutes. Critical steps include (1) obtaining a satisfactory specimen and preparing a satisfactory smear (this can be checked before or after staining), (2) drying the specimen properly before fixing it, (3) using a high-quality fluorescence microscope, and (4) obtaining and maintaining an experienced microscopist who can recognize elementary bodies and artifacts.

Compared with culture, the sensitivity of the direct smear test is $\geq$ 90% in most published studies, and the specificity is $\geq$ 98%. The positive predictive value of this test has ranged from approximately 80% in populations with a *Chlamydia* prevalence of 10% to 95% in populations with a prevalence of 30% (*32*). Lower sensitivities and specificities are often encountered in situations in which specimens are less than optimal or individuals reading the slides are relatively inexperienced. In these instances, assessment of the proficiency of laboratory

*They are Microtrak, manufactured by Syva Diagnostics, and Chlamydiazyme, manufactured by Abbott Diagnostics. (Use of trade names is for identification only and does not imply endorsement by CDC or the U.S. Public Health Service.)

techniques is essential. This can be accomplished by comparing results with those obtained with tissue culture or by exchanging slides with a central reference laboratory that does proficiency testing.

The major advantages of the direct smear test are (1) the uncomplicated transport and storage of specimens, (2) rapid processing time compared with that required for other methods (*33*), (3) a high specificity, and (4) the ability to check on adequacy of specimen collection (i.e., cells on the slide). Disadvantages of the method are (1) the requirement for precise specimen collection, (2) the need for high-quality fluorescence microscope equipment, (3) the need for an experienced microscopist, and (4) the relatively labor-intensive nature of the process.

Enzyme Immunoassay (*34*)

This test measures antigen-antibody reactions through an enzyme-linked immunoabsorbent assay (ELISA) and requires a spectrophotometer. Processing time for specimens is approximately 4 hours.

Questions continue to be raised about the reliability of available EIAs for *C. trachomatis*. The sensitivity of the test has varied from 67% to 90%, the specificity from 92% to 97%, and the positive predictive value from 32% to 87%, depending on the population studied (*35*). Much of the observed disparity has been attributed to variable sensitivity of the tissue culture systems against which the EIA has been compared.

The advantages of the EIA are (1) the uncomplicated transport and storage of specimens, (2) the objective method of measurement in the laboratory, which involves standard equipment and does not depend upon a specially trained observer, and (3) the ability to test large numbers of specimens at a time.

The disadvantages are that (1) the adequacy of the specimen cannot be checked and (2) the test cannot be performed while the patient is waiting (although this is also true for the direct smear test if no fluorescence microscope is available).

It is not known whether either method of antigen detection can be used for specimens from sites other than the eyes and genitals (e.g., pharynx).

Serology

Currently, *Chlamydia* serology has little value in routine clinical management and basically remains a research tool. Although some serologic tests are commercially available, they have not been shown to be useful in routine diagnosis.

There are two standard methods—complement fixation and microimmunofluorescence (MIF) (*35*). ELISA tests have been developed, but none are recommended for wide use (*36,37*). The only valid clinical uses of serologic tests are in infant pneumonia, where specific immunoglobulin M (IgM) MIF serology, when available, is the diagnostic test of choice; and in occasional cases of suspected lymphogranuloma venereum (LGV). The difficulties in preparing the antigen and conducting the test restrict the use of the test to a limited number of research laboratories.

Diagnostic Considerations

The value of rapid diagnostic tests for detecting *C. trachomatis* infection depends primarily on the prevalence of disease in the population tested and the availability of other tests. For low-risk groups, the predictive value of a positive test is lower than for high-prevalence populations, even if the test is highly sensitive and specific. For example, in a population with a 5%

prevalence, a rapid test with a 95% specificity and sensitivity will have a predictive value positive of 50% (meaning that there is only a 50% chance that an individual who is diagnosed as having disease actually has it). In situations in which an increase in the predictive value of a positive test is desired, in order to lower risks of incorrectly labeling persons as having STD, positive screening tests can be confirmed by culture, or culture methods can be used for screening (with an accompanying rise in cost). As new tests become available, physicians, hospital and commercial laboratorians, and public health program directors must be aware of the sensitivity, specificity, and predictive value of such tests when determining whether to use them in specific situations.

As more laboratories begin to do diagnostic testing for *Chlamydia*, laboratory quality control assumes increasing importance. Each laboratory should verify the accuracy of test methods other than culture by periodically comparing results with those obtained using cultures. Such comparisons are particularly important when the laboratory implements a new test method. Laboratories that do cell-culture isolation of *Chlamydia* should run appropriate positive and negative controls to verify sensitivity of the cell cultures being used and should periodically evaluate the effectiveness of transport systems. Regional reference laboratories should be established for verification of culture results or evaluation of unexpected or discrepant results. Proficiency testing programs should be developed for culture and other test methods so that laboratories can evaluate their methods using unknown specimens.

Patient Management

High-Risk Groups

High-risk groups should be defined using demographic profiles and the estimated or established prevalence of chlamydial infection in a particular community or patient population. Although the criteria described under Risk Assessment can be used as a guide to establishing a high-risk profile, local determinants of risk are more precise and should be identified if possible. Local data also provide more accurate baseline prevalences, against which the success of prevention and control strategies can be measured.

When culture results are available, they should be used in decisions concerning appropriate therapy. However, undiagnosed patients who fit an established high-risk profile should also be offered treatment, unless local or individual circumstances dictate otherwise. Patients in the following groups should immediately receive a regimen that includes effective treatment against *C. trachomatis* infection.

Symptomatic Syndromes Associated with *Chlamydia*

Persons with symptoms of the following *Chlamydia*-associated syndromes should receive treatment for chlamydial infection:

1. Nongonococcal urethritis (NGU)
2. Mucopurulent cervicitis (MPC)
3. Pelvic inflammatory disease (PID)
4. Epididymitis (men $\leq$ 35 years of age)

Because MPC, PID, and epididymitis are also commonly associated with *N. gonorrhoeae*, patients with these syndromes should also receive treatment effective against gonococcal infection.

Asymptomatic Contacts of Syndromes Associated with *Chlamydia*

Individuals exposed through sexual contact with patients who have any of the above symptomatic syndromes (within 30 days of the onset of their symptoms or clinical evaluation) should be evaluated for STD and treated for presumptive chlamydial infection.

Gonococcal Infection

Women with confirmed *N. gonorrhoeae* infection of the endocervix, heterosexual men with diagnosed gonococcal infection of the urethra, and sex partners of members of both of these groups of patients should be treated with an antimicrobial regimen that is effective against both *N. gonorrhoeae* and *C. trachomatis* infection.

Screening

Selective screening to detect asymptomatic infection is an essential component of a successful control program. Whenever possible, criteria for routine screening should be based on local determinants of risk. An appropriate diagnostic method must be selected. Diagnostic considerations for current tests/methods are discussed above. The following guidelines are provided to assist in determining which test to use.

Screening Criteria

No single individual characteristic or practice (see p. 55S), is in itself a sufficient criterion to define which persons should be screened. However, a composite of individual factors, in conjunction with a community factor such as type of health-care facility (see p. 56S), will help to maximize yield from screening. Consequently, available evidence leads to the recommendation that the priorities for routine screening shown below be used.

STD Clinic

1. Individuals attending STD clinics who otherwise would not be offered antichlamydial treatment should be screened first. (The screening of asymptomatic, high-risk women should be accorded the highest priority. In general, the screening of heterosexual men should have a higher priority than screening homosexual men.)

2. Individuals with symptomatic syndromes associated with *Chlamydia* should be screened next. (Screening of women should be accorded higher priority than screening of men.)

Other High-Risk Health-Care Facility

Health-care facilities other than STD clinics may also have a high prevalence of chlamydial infections. In particular, many adolescent and family planning clinics are categorized as high-risk centers, but a wide disparity in rates of chlamydial infection may be observed in different populations.* Facilities that serve high-risk populations should follow the order of screening

*Other health-care sites (i.e., some private practices, community health clinics, hospital emergency rooms) may also be high-risk facilities but have not yet been investigated. For now, practitioners are urged to base their screening decisions on the prevalence of individuals, particularly women, with high-risk patient profiles and on relevant local information.

priority for STD clinics above; those serving undetermined or low-risk populations should follow the priority below for Undetermined/Low-Risk Health-Care Facility.

Undetermined/Low-Risk Health-Care Facility

1. Persons in urban settings who are younger, have lower socioeconomic status, and have multiple sex partners, and who otherwise would not be offered antichlamydial treatment, should be screened first. (In this category of high-risk patients, women should be accorded highest priority for screening.)
2. Individuals with symptomatic syndromes associated with *Chlamydia* should also be screened. (Screening of women should be accorded higher priority than screening of men.)

Diagnostic Method

Culture and two different antigen detection tests are currently the only diagnostic methods acceptable for screening for *Chlamydia* infection. Culture remains the most accurate method, but is costly and takes at least 2-3 days before results are available. Antigen detection tests have emerged as reasonable alternatives, but questions remain about their reliability for low-prevalence populations. Following are guidelines for the use of diagnostic tests in screening:

1. Culture, based upon availability, is the preferred method for routine screening.
2. Direct smear using fluorescent antibody (DFA) is the most thoroughly evaluated alternative to culture. However, optimal results with the currently marketed test have been achieved for high-risk women and symptomatic men by very experienced research laboratories. For other populations, test results obtained by less experienced technologists may not be as reliable. Consequently, DFA results should be compared periodically with those obtained through culturing.
3. Enzyme immunoassays have not been as completely evaluated as the DFA tests. The currently marketed test probably is less sensitive and specific than DFA, but the quality of results is also less likely to depend on the level of experience of laboratory personnel. It is important that regional reference laboratories be available to monitor the performance of these and other new antigen detection tests and to advise about appropriate applications and quality control problems.
4. Pap smears are not sufficiently sensitive or specific to use routinely for screening for chlamydial infections. However, female patients whose Pap smears show certain inflammatory changes should have a diagnostic test specific for *Chlamydia*.

Special Groups

Pregnant Patients

Certain groups of pregnant women are at high risk of chlamydial infections. Transmission to the newborn is a well-established consequence of these infections. The precise effects of chlamydial infection on pregnancy outcome are uncertain, and studies are under way to resolve this issue.

Recommendation

Screening is suggested at the first prenatal visit for the following groups of pregnant women:

1. Adolescents (< 20 years of age)

2. Unmarried women
3. Married women who may be at high risk because of multiple sex partners or a history of other STD

Screening of pregnant women who fall into any of these high-risk categories in inner-city hospitals is particularly important because of the high prevalence of asymptomatic infections among the patients served by these facilities.

Neonates

Ophthalmia Prophylaxis

None of the presently recommended approaches for prophylaxis against gonococcal and chlamydial ophthalmia neonatorum is completely effective. Silver nitrate is effective in preventing gonococcal infections but does not prevent chlamydial disease and frequently causes chemical conjunctivitis. Erythromycin is effective in preventing both gonococcal and chlamydial ophthalmia and does not cause chemical conjunctivitis, but the topical use of this drug does not prevent nasopharyngeal chlamydial infection or pneumonia. Furthermore, erythromycin prophylaxis is considerably more expensive than silver nitrate prophylaxis. Tetracycline ointment has not been as extensively evaluated as has erythromycin but appears to be as effective. Whichever type of prophylaxis is used should be implemented no later than 1 hour after birth—preferably immediately after delivery since delayed application may reduce efficacy.

Recommendation

Erythromycin (0.5%) ophthalmic ointment, tetracycline (1%) ointment, or silver nitrate should be instilled into the eyes of all neonates as soon as possible after delivery and never later than 1 hour after birth. Single-use tubes or ampules are preferable to multiple-use tubes.

Neonatal Infection

Eighteen to fifty percent of infants born to infected mothers will have conjunctivitis between 1 and 3 weeks after birth (*7*). The symptoms are often mild, and the disease may be missed unless looked for carefully. Though considerable morbidity results acutely from the severe form of this disease, it is self-limited and does not appear to result in loss of vision. Three to eighteen percent of infants born to infected mothers will develop chlamydial pneumonia/bronchiolitis, usually at 1-4 months of age (*7*). In most cases this is a mild disease, but it can be severe and require hospitalization.

Recommendation

Screening for neonatal infection is not indicated. Newborns with conjunctivitis and afebrile pneumonia/bronchiolitis should have specimens culture-tested for *C. trachomatis* and be appropriately treated as recommended below. If cultures are positive, mothers (and their sex partners) of the infected children should also be treated.

Treatment Regimens

CONFIRMED INFECTIONS

Uncomplicated Urethral, Endocervical, or Rectal Infection in Adults

Drug Regimens of Choice

Tetracycline hydrochloride (HCl): 500 mg, by mouth, 4 times a day for 7 days.

OR

Doxycycline hyclate: 100 mg, by mouth, 2 times a day for 7 days.

Alternative Regimens

(for patients for whom tetracyclines are contraindicated or not tolerated)

Erythromycin base or stearate: 500 mg, by mouth, 4 times a day for 7 days, or **erythromycin ethyl succinate:** 800 mg, by mouth, 4 times a day for 7 days.

Sulfonamides are also active against *C. trachomatis*. Although optimal dosages of sulfonamides for chlamydial infection have not been defined, sulfamethoxazole, 1 g by mouth, twice a day for 10 days, is probably effective.

Follow-Up

When taken as directed, the tetracycline and erythromycin regimens listed above are highly effective (> 95% cure rates). No tetracycline-resistant *Chlamydia* has been described. Post-treatment cultures are not advisable if laboratory resources are limited. A positive post-treatment culture is more likely to represent noncompliance with treatment, failure to treat sex partners, or laboratory error than resistance to the antibiotic. Patients who do have positive post-treatment cultures should be treated again according to one of the above regimens.

Management of Sex Partners

All persons sexually exposed to *C. trachomatis* infection (within 30 days after their sex partner develops symptoms or has a positive clinical evaluation) should be examined for STD and promptly treated for *C. trachomatis* with one of the above regimens. This group includes sex partners of individuals with sexually acquired chlamydial infection, mothers of infected newborns, and the sex partners of these mothers.

Urogenital Infections during Pregnancy

Drug Regimen of Choice

Erythromycin base: 500 mg, by mouth, 4 times a day for 7 days, or **erythromycin ethyl succinate:** 800 mg, by mouth, 4 times a day for 7 days.

Erythromycin stearate in appropriate doses may also be effective, but has not been adequately studied.

Alternative Regimen

(for female patients who cannot tolerate the above regimen, a decreased daily dose is recommended)

Erythromycin base: 250 mg, by mouth, 4 times a day for 14 days.

The optimal dose and duration of antibiotic therapy for pregnant women have not been established. Currently, there are no completely acceptable alternative regimens for female patients who are allergic to erythromycin or otherwise cannot tolerate erythromycin. In the case of proven treatment failure, the patient should be re-treated with erythromycin according to either of the dosage schedules outlined above.

Established Conjunctivitis of the Newborn*

Drug Regimen of Choice

Oral erythromycin syrup: 50 mg/kg body weight/day in 4 divided doses for 14 days.

There is no indication that topical therapy provides additional benefit. If inclusion conjunctivitis recurs after therapy, erythromycin treatment should be reinstituted for an additional 1-2 weeks.

Pneumonia among Infants

Drug Regimen of Choice

Oral erythromycin syrup: 50 mg/kg/day in 4 divided doses for 14 days.

CHLAMYDIA-ASSOCIATED SYNDROMES

Nongonococcal Urethritis

NGU can be diagnosed for a male patient if tests for *N. gonorrhoeae* are negative and the patient has objective evidence of urethritis. Objective evidence of urethritis includes a visibly abnormal discharge, pyuria defined as > 10 polymorphonuclear leukocytes (PMN) per high dry field in the sediment of a first-voided urine specimen, or > 4 PMN per oil immersion field in a Gram-stained urethral smear. Approximately 50% of the cases of urethritis not associated with *N. gonorrhoeae* are caused by *C. trachomatis*. NGU requires prompt antimicrobial treatment of the patient and evaluation and treatment of any sex partners.

Drug Regimens of Choice

Tetracycline HCl: 500 mg, by mouth, 4 times a day for 7 days.

OR

Doxycycline: 100 mg, by mouth, twice a day for 7 days.

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*For all cases of neonatal conjunctivitis, an appropriate test should be done to rule out infection with *N. gonorrhoeae*.

Alternative Regimen

(for patients for whom tetracyclines are contraindicated or not tolerated)

Erythromycin base or stearate: 500 mg, by mouth, 4 times a day for 7 days, or **erythromycin ethyl succinate**: 800 mg, by mouth, 4 times a day for 7 days.

Sulfonamides are not suitable for treatment for clinical syndromes when *Chlamydia* cultures are not performed, since they may not be effective against *Ureaplasma urealyticum* and other organisms that cause nonchlamydial genital infection.

Management of Sex Partners

All persons who are sex partners of patients with NGU (within last 30 days) should be examined for STD and treated promptly with one of the above regimens.

Follow-Up

Patients should be advised to return for follow-up medical care if symptoms persist or recur.

Mucopurulent Cervicitis*

The presence of mucopurulent endocervical exudate often reflects cervicitis due to chlamydial and/or gonococcal infection. If *N. gonorrhoeae* is found on Gram stain or culture of endocervical or urethral discharge, a treatment regimen effective against both gonococcal and chlamydial infection should be used. When only chlamydial infection is proven or suspected, therapy should consist of one of the regimens below.

Drug Regimens of Choice

Tetracycline HCl: 500 mg, by mouth, 4 times a day for 7 days.

OR

Doxycycline: 100 mg, by mouth, twice a day for 7 days.

Alternative Regimens

(for patients for whom tetracyclines are contraindicated or not tolerated)

Erythromycin base or stearate: 500 mg, by mouth, 4 times a day for 7 days, or **erythromycin ethyl succinate**: 800 mg, by mouth, 4 times a day for 7 days.

Management of Sex Partners

Men exposed to women with MPC attributed to chlamydial infection should be evaluated for STD and treated with one of the above regimens. If *N. gonorrhoeae* is found, treatment should be with a regimen effective against uncomplicated gonococcal and chlamydial infection.

*Criteria for presumptive diagnosis include (1) *mucopurulent secretion* from the endocervix, which is usually yellow or green when viewed on a white cotton-tipped swab (positive swab test); (2) $\geq$ 10 *polymorphonuclear leukocytes* per microscopic oil immersion field (X 1,000) in a Gram-stained smear of endocervical secretions; and (3) *cervicitis*, determined by cervical friability (bleeding when the first swab culture is taken) and/or by erythema or edema within a zone of cervical ectopy.

Pelvic Inflammatory Disease

(Endometritis, Salpingitis, Parametritis, and/or Peritonitis)

Acute PID refers to the acute clinical syndrome attributed to the ascending spread of microorganisms, unrelated to pregnancy or surgery, from the vagina and endocervix to the endometrium, fallopian tubes, and/or contiguous structures. Clinical findings for most patients with PID include lower abdominal tenderness, adnexal tenderness, and pain induced by lateral motion of the uterine cervix. Many cases of PID are caused by more than one organism. Causative agents include *C. trachomatis*, *N. gonorrhoeae*, anaerobic bacteria (including Bacteroides and gram-positive cocci), and facultative gram-negative rods (such as *Escherichia coli*), *Actinomyces israelii*, and *Mycoplasma hominis*.

These agents cannot usually be differentiated in individual patients. Consequently, treatment regimens should be used that are active against the broadest range of the pathogens. CDC has already published comprehensive guidelines regarding criteria for hospitalization, rationale for selection of antimicrobials, and general treatment regimens for the major pathogens associated with PID (*39*).* Below are examples of specific combinations of regimens for optimal coverage for *C. trachomatis* and for adequate coverage for the other common causative agents.

Inpatient Treatment

Doxycycline: 100 g, intravenous (IV), 2 times a day.

PLUS

Cefoxitin: 2.0 g, IV, 4 times a day.

Continue drugs IV for at least 4 days and at least 48 hours after patient improves. Continue doxycycline 100 mg, by mouth, 2 times a day, to complete 10-14 days of therapy.

Ambulatory Treatment

Cefoxitin: 2.0 g, intramuscular (IM), OR **amoxicillin**: 3.0 g, by mouth, OR **ampicillin**: 3.5 g, by mouth, OR **aqueous procaine penicillin G**: 4.8 million units, IM, at 2 sites (each along with **probenecid**: 1.0 g, by mouth), OR **ceftriaxone**: 250 mg, IM

FOLLOWED BY

Doxycycline: 100 mg, by mouth, 2 times a day for 10-14 days.

Tetracycline HCl 500 mg, by mouth, 4 times a day, can also be used, but is less active against certain anaerobes and requires more frequent doses; both factors represent drawbacks in treatment of PID.

Management of Sex Partners

All persons who are sex partners of patients with PID (within the 30 days prior to onset of their symptoms or positive clinical evaluation) should be examined for STD and treated promptly with a regimen effective against uncomplicated gonococcal and chlamydial infection.

*A CDC update of these Guidelines is in press.

Follow-Up

All patients treated as outpatients should be clinically reevaluated in 48-72 hours. Those not responding favorably should be hospitalized. Patients should also be reevaluated after they complete treatment.

Intrauterine Device

The intrauterine device (IUD) is a risk factor for the development of PID. Although the exact effect removing an IUD has on the response of acute salpingitis to antimicrobial therapy and on the risk of recurrent salpingitis is unknown, it is recommended that the IUD be removed as soon as possible after antimicrobial therapy has been initiated. When an IUD is removed, contraceptive counseling is necessary.

Acute Epididymo-Orchitis

Acute epididymo-orchitis has two forms: (1) a sexually transmitted form usually associated with urethritis and commonly caused by *C. trachomatis* and/or *N. gonorrhoeae* and (2) a nonsexually transmitted form associated with urinary tract infections caused by Enterobacteriaceae or other nonsexually transmitted uropathogens. Urine should be examined by Gram stain and culture to exclude bacteruria in all patients, including those with urethritis. An important part of the differential diagnoses is testicular torsion, a surgical emergency.

Sexually transmitted epididymo-orchitis usually affects young adults and is associated with presence of clinical or subclinical urethritis, absence of underlying genitourinary pathology, and absence of gram-negative rods on Gram stain of urine.

Drug Regimens of Choice

Amoxicillin: 3.0 g, by mouth, OR **ampicillin**: 3.5 g, by mouth, OR **aqueous procaine penicillin G**: 4.8 million units, IM at 2 sites (each along with **probenicid**: 1.0 g, by mouth), OR **spectinomycin**: 2.0 g, IM, OR **ceftriaxone**: 250 mg, IM

FOLLOWED BY

Tetracycline HCl: 500 mg, by mouth, 4 times a day for 10 days.

OR

Doxycycline: 100 mg, by mouth, 2 times a day for 10 days.

Alternative Regimens

(for patients for whom tetracyclines are contraindicated or not tolerated)

Erythromycin base or stearate: 500 mg, by mouth, 4 times a day for 7 days, or **erythromycin ethyl succinate**: 800 mg, by mouth, 4 times a day for 7 days.

Management of Sex Partners

Sex partners of patients with sexually transmitted acute epididymo-orchitis (diagnosed within 30 days of exposure) should be examined for STD and promptly treated with a regimen effective against uncomplicated gonococcal and chlamydial infection.

Follow-Up

Failure to improve within 3 days requires reevaluation of diagnosis/therapy and consideration for hospitalization.

Patient Education

Patient Counseling

The effective management of chlamydial infection includes counseling of patients. Such counseling should be designed to influence specific behavior that will contribute to successful therapy, disease intervention, and prevention. Patient handouts designed for easy comprehension are an efficient way of conveying basic information. These messages should be reinforced by practitioners through discussions with patients that are tailored to the individual and provide an opportunity for questions.

Recommendation

Practitioners should provide counseling to patients regarding their disease, its treatment, and the overall responsibility of the patient in the process. Information conveyed to patients should at least include:

1. Instructions for taking medication, including the dosage, timing, and length of the regimen. Patients must clearly understand that they must continue to take medication according to schedule, despite abatement of symptoms.
2. Advice regarding follow-up for side effects or other difficulty with medication, continued or worsened symptoms, and test of cure, if indicated.
3. Suggestion to abstain from sexual activity until medication is completed by both patient and partner. If this is not possible, patients should be encouraged to use condoms until treatment is completed.
4. Suggestion to cease sexual activity immediately if the same or other STD symptoms recur, and to return to the practitioner/clinic with the steady sex partner.
5. Suggestion to regularly use barrier methods, particularly condoms, to prevent chlamydial infection and other STD.

Sex Partner Referral

The sex partners of patients with chlamydial infection should be referred for medical care through the efforts of individual patients, or through a disease intervention specialist (DIS). Although the latter process is time-consuming, it may be very effective. However, locating and referring sex partners through a DIS is clearly not feasible for all patients with chlamydial infection and the *Chlamydia*-associated syndromes discussed above. First priority for interviewing/counseling efforts by a DIS should be given to patients with proven chlamydial infection. The contract method of sex partner referral should be used, with the patient assuming referral responsibility whenever possible. The referral of sex partners by the patient is a more practical approach in terms of human resources, but the effectiveness of this practice has not been evaluated among *Chlamydia* patients. Nevertheless, attempts must be made to capitalize on patients' knowledge of and persuasiveness with their own sex partners.

Recommendation

Patients with chlamydial infection should be encouraged to refer all persons with whom they had sexual encounters in the 30 days prior to onset of their symptoms or clinical evaluation. (Approximately 94% of sex partners to NGU patients brought to treatment have been exposed within 30 days.)

Prevention

Of all possible *Chlamydia* control approaches, successfully preventing the initial infection remains the most effective. Education of the public and of health professionals is essential for prevention at all three levels (primary, secondary, tertiary), especially in the absence of an effective vaccine.

Professional Training/Education

Providers of health care can play a leading role in reducing the incidence of *C. trachomatis* infection and its complications. Timely diagnosis and appropriate treatment of chlamydial infection by practitioners will prevent further transmission and minimize the risk that the infected individual will have adverse consequences. Additionally, clinicians are in a position to influence a patient to avoid behavior likely to result in transmitting disease or in being reinfected. STD education for health-care professionals should promote the following:

1. Recognizing *Chlamydia*-associated syndromes and high-risk patients.
2. Following recommended STD treatment guidelines.
3. Reporting cases promptly and completely.
4. Counseling patients to refer all sex partners for medical evaluation, to take all medication as prescribed, and to modify their behavior so as to reduce the risk of future infection.

Recommendation

1. Professional recognition should be enhanced by incorporating knowledge about chlamydial infection into education and training programs for physicians, nurses, laboratory personnel, and allied health professionals (such as physician assistants).
2. Organizations for health professionals, academic centers, colleges, and societies should be encouraged to formally support the chlamydial prevention and control efforts by (a) providing appropriate continuing medical/professional education courses about chlamydial infections at national/regional/local meetings and (b) encouraging health-professional journals—especially official organizational publications—to publish chlamydial policy guidelines and clinical reviews and research papers on *Chlamydia* and associated infections.

Public Education/Health Promotion

Education of the public is necessary to provide a high level of awareness of chlamydial infections (and other STD) and to influence people to know and communicate about the prevention, recognition, and treatment for *Chlamydia*; to support control efforts; and to reduce their personal risk of acquiring or transmitting a chlamydial infection. Accumulating evidence suggests that public education can influence individuals to reduce their risk of acquiring an STD by changing sexual practices.

One such practice that should be encouraged is the use of barrier methods of contraception. Barrier methods of contraception (condoms and diaphragms) are known to provide protection against *Chlamydia* infection and other STD when used properly. The effectiveness of spermicides in preventing *Chlamydia* infection has not been determined. However, spermicides do not enhance infection and do achieve some measure of protection when used in conjunction with a diaphragm or condom.

Recommendation

Disseminate the following information to the public:

1. Risks of chlamydial infection associated with sexual activity, especially when multiple partners are involved.
2. Role of barrier methods of contraception for personal prophylaxis to prevent chlamydial infection and other STD.
3. Symptoms of chlamydial infection and the need to seek appropriate medical care immediately.
4. Importance and frequency of asymptomatic chlamydial infection.
5. Sources of appropriate medical care for chlamydial infection and other STD.
6. Importance of compliance with treatment and behavioral recommendations.
7. Sequelae of untreated chlamydial infection and other STD, such as PID, infertility, ectopic pregnancy, and infant morbidity.

Surveillance

A fundamental requisite for control and prevention of chlamydial infection is a national surveillance system, since it provides quantitative estimates of incidence and prevalence, a basis for determining secular trends, and a tool for evaluating control efforts. Current methods for diagnosis now permit the establishment of a multitiered, multifocal disease surveillance system. The tiers are local, state, and national. The foci include subgroups at special risk, clinical syndromes of particular importance, and the general population.

A national surveillance system will require state reporting laws and/or regulations to provide the necessary support for prevention activities. Reporting laws promote and legitimize the involvement of public health authorities in assuring adequate individual patient management—including referral of sex partners—and may facilitate other activities such as screening and education. Moreover, case reporting provides a uniform basis for describing the extent and trend of disease.

Prevention and control activities for chlamydial infections have been proposed in this document, although the inadequacies in current diagnostic methods are acknowledged. In particular, patient management, including sex partner referral, is recommended for selected *Chlamydia*-associated clinical diagnoses (not dependent on the results of a laboratory test for *Chlamydia*). Similarly, case reporting should include selected clinically diagnosed conditions associated with *Chlamydia* infection in addition to laboratory-diagnosed *Chlamydia* infection. Pending development of nationwide laboratory capability for identifying *Chlamydia*, conditions should be selected that will best serve as indices for chlamydial infection, and that represent important public health problems in their own right. Reporting of clinically diagnosed conditions should augment rather than replace reporting of laboratory-diagnosed problems, since continuing efforts to develop a national laboratory capability will greatly enhance opportunities for ongoing improvements in patient management and public health interventions.

Although a national surveillance system should be based on case reporting, additional approaches, involving classical statistical methods, should be utilized, at least at the national level, to provide extent and trend estimates less vulnerable to the biases inherent in estimates based on case reports.

Recommendation

A national system for surveillance of *Chlamydia*-associated disease should be established, to provide epidemiologic detail appropriate to local, state, and national reporting tiers. The surveillance system should include the following elements:

1. Disease reporting

Information on *Chlamydia*-associated morbidity should be accumulated on a national level. States are encouraged to require reporting of specific entities and to transmit appropriate surveillance data to CDC. The suggested entities are:

a. Laboratory-diagnosed chlamydial infection
b. Nongonococcal urethritis (NGU)*
c. Pelvic inflammatory disease/acute salpingitis (PID/AS)*

2. Additional approaches

National surveys of health-care providers, involving probability sampling, should continue to be utilized to obtain estimates of the number of diagnoses for *Chlamydia*-related conditions. These include the IMS National Disease and Therapeutic Index survey of office-based practitioners and the National Centers for Health Statistics National Hospital Discharge Survey. Surveys of other outpatient sources of care (e.g., STD clinics and emergency rooms), or sentinel reporting systems should be developed whenever feasible.

*No absolute criteria exist for defining the clinical syndromes of NGU and PID/AS, but a constellation of signs and symptoms may be suggestive. For NGU, these include a patient with dysuria, white cells on Gram stain of urethral smears, and/or frank urethral discharge, in the presence of negative tests for gonorrhea. PID/AS is more protean in its manifestations, and the diagnosis ultimately rests on the judgment of the attending clinician. Usual features include a combination of (1) lower abdominal pain, (2) adnexal tenderness, (3) adnexal mass, (4) pain on cervical motion, (5) mucopurulent discharge, and (6) temperature elevation. No single combination is pathognomonic.

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